Influence of dystonia on the response to long-term L-dopa therapy in Parkinson's disease

COLIN J. ANDREWS

From the Division of Neurology, the Prince Henry Hospital, Little Bay, N.S.W. 2036, Australia

SUMMARY The gait of normal subjects was examined electromyographically and the pattern was altered during preferential blockade of large nerve fibres to alternating activity in flexor and extensor muscles. The EMG activity was disrupted more in flexor than extensor muscles by preferential ischaemic blockade. Normal gait was associated with flexor contraction only when the foot was lifted and placed on the ground, whereas during ischaemic blockade flexor contraction continued during the interval between foot lifting and foot placement.

The 'freezing' or 'blocking' gait in Parkinson's disease was found to be associated with co-activation of flexor and extensor muscles and this phenomenon occurred only in patients with features of flexion dystonia in the electromyographic recordings of their tonic stretch reflexes. Eight of nine patients with evidence of flexion dystonia showed a deterioration in their response to L-dopa therapy over a two year period, whereas four patients without flexion dystonia maintained their clinical improvement.

The term dystonia implies a disorder of the extrapyramidal system in which the limbs become fixed in an abnormal posture as the result of synchronous activity in the antagonistic muscles operating at a joint. Denny-Brown (1962, 1968) has described three fundamental patterns of dystonic postural fixation—namely, hemiplegic dystonia, flexion dystonia (as seen in Parkinson's disease), and torsion dystonia (as in dystonia musculorum deformans). Recently, Yanagisawa and Goto (1971) have analysed dystonia musculorum deformans electromyographically and found that 'tonic non-reciprocal involuntary innervation appeared in both agonists and antagonists at rest', and that this coactivation 'was intensified by assumption of any active posture'. In an electromyographic analysis of rigidity in Parkinsonism Andrews, Burke, and Lance (1973) noted that the static and dynamic tonic stretch reflexes of hamstrings and quadriceps muscles became maximal while the knee was still in a slightly flexed position in some patients. These authors were unable to explain this phenomenon on any known segmental mechanism and suggested that it might be a manifestation of flexion dystonia. This characteristic response was not altered by successful L-dopa therapy (Andrews and Burke, 1972) despite a dramatic reduction in rigidity judged both clinically and electromyographically. It was observed that 'freezing' of gait reappeared and then became worse during long term therapy with L-dopa in a large proportion of patients. Unpublished observations on the electromyographic abnormalities of 'freezing' or 'blocking' gait in Parkinson's disease revealed co-activation of agonist and antagonist in the lower limbs, a classical feature of dystonia. The relationship between flexion dystonia, the 'freezing' gait of Parkinson's disease and the long term response over at least two years of L-dopa therapy forms the substance of the present study. Because of the relatively small amount of information available about muscle contraction during walking in normal subjects, an electromyographic study of normal gait was undertaken as a preliminary to the analysis of

1 Edwin and Daisy Street Research Fellow in Neurology. Address for reprints: as above.
records obtained from patients with Parkinson's disease.

METHODS

The tonic stretch reflexes of the hamstring and quadriceps muscles were analysed electromyographically in 17 patients with Parkinsonism, the subject of a previous study (Andrews, Burke, and Lance, 1972). Of the 17 patients, two failed to respond to L-dopa therapy by both clinical and by electromyographic criteria and in a further two patients L-dopa therapy was suspended because of toxic side-effects. The remaining 13 patients with Parkinsonism participated in a trial of L-dopa for at least two years and were analysed electromyographically before and at intervals during L-dopa therapy. All patients showed clinical signs of rigidity, bradykinesia, and exaggerated physiological tremor and four patients had an additional alternating tremor. The 13 patients were aged 53 to 69 years; 12 were male and one female. Six had previously been subjected to thalamotomy, unilateral in three and bilateral in three. The Webster rating scale (Webster, 1968) was used to score disability up to a maximum of 30 points for the most severely affected patients. The normal subjects whose gait was studied electromyographically were aged 23 to 29 years, three male and one female.

The gait of five patients with Parkinsonism was examined. Four had frequent episodes of freezing that could be induced by startle or walking around a chair and one patient had severe rigidity without induced or spontaneous freezing of gait. The gait in the four normal subjects was examined before, during, and after preferential block of large afferent nerve fibres by peripheral ischaemia. Ischaemia was induced by a sphygmomanometer cuff inflated to 200 mm Hg. The cuff was placed immediately below the hip joint and ischaemia was maintained until the ankle jerk was abolished clinically and electromyographically. This occurred after about 23 to 25 minutes. Recordings were then taken for about two to three minutes during which time joint position sense of the toes and ankle was tested.

The electromyogram (EMG) produced by walking was recorded by pairs of surface electrodes 10 cm apart over the relevant muscles. Field spread of EMG potentials from the antagonistic muscle was checked during active contraction of the agonist while monitoring EMG of both muscles on an oscilloscope. The EMG potentials were amplified, fullwave rectified, displayed on an oscilloscope, and photographed with a Polaroid oscilloscope camera or were integrated (time constant 1.2 sec) and recorded on a four channel type S Offner Dynograph.

Foot lifting and placement was recorded by strapping an accelerometer to the dorsum of the foot and was recorded along with the EMG potentials.

TERMINOLOGY

FLEXION DYSTONIA The presence of flexion dystonia was determined from electromyographic recordings taken before the start of L-dopa therapy (Andrews et al., 1972). Patients in whom the static and dynamic tonic stretch reflexes of the hamstrings muscles were maximal at a partially flexed position of the knee were classified as having flexion dystonia, whereas patients whose hamstrings tonic stretch reflexes were maximal at the fully stretched position were placed in the non-dystonic group.

FIG. 1. EMG recordings of normal gait demonstrating the difference in pattern of muscle contraction between flexors and extensors of the knee and those of the ankle. Muscle contraction of quadriceps (QUADS) accompanies heel placement ( ), whereas muscle contraction of gastrocnemius-soleus continues while the foot is on the ground. Foot lifting ( ) is associated with EMG activity in tibialis anterior (TA) but not in hamstrings (HAM).

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THE WALKING CYCLE  Philipson (1905) divided the step cycle in the dog into one flexion phase and three extension phases. The flexion phase starts with the lifting of the foot (indicated by upward pointing arrow in illustrations) and ends when extension begins in the knee and ankle. This extension occurs when the leg is still in the air (swing phase) and was termed the first extension phase. The second and third extension phase occur as the foot is placed on the ground (downward arrows in all Figures).

RESULTS

NORMAL GAIT AND ITS RESPONSE TO ISCHAEMIC PREFERENTIAL LARGE FIBRE BLOCK

EXTENSOR MUSCLES  The EMG activity of quadriceps differed from that of gastrocnemius-soleus during the walking cycle. In quadriceps, EMG activity occurred in the first extension phase, and increased in the second extension phase (Fig. 1). In the gastrocnemius-soleus muscle EMG activity was absent or of very short duration in the first extension phase and showed little alteration between the second and third extension phases. The EMG activity in the third extension phase often ceased before the foot was lifted.

Peripheral ischaemia for 23 to 25 minutes was sufficient to block the ankle jerk and during this state of preferential block of large afferent nerve fibres the subject was aware of loss of proprioception while walking despite preservation of joint position sense to clinical testing. The loss of proprioception was reflected in the oscillation of the accelerometer trace recorded during foot lifting and foot placement (flexion and first extension phase) (Fig. 2).

The EMG activity in gastrocnemius-soleus became pronounced in the first extension phase and was maintained longer in the third extension phase, being present until foot lifting occurred.

FLEXOR MUSCLES  The EMG of the flexors of the knee and dorsiflexors of the ankle also showed differences during walking. Foot lifting was always associated with EMG activity in tibialis anterior but not usually in hamstrings, irrespective of the speed of walking (Fig. 1). Occasional subjects showed EMG activity in tibialis anterior before foot lifting but this was absent in some walking cycles and appeared only rarely in most subjects. Foot placement was always associated with EMG activity in flexors of the knee and ankle. Preferential ischaemic block appeared to disrupt the EMG activity in flexors more than extensors. The most consistent feature was the maintenance of EMG activity between foot lifting and foot placement (Fig. 2).

PARKINSONIAN GAIT AND THE PHENOMENON OF 'FREEZING'

The gait of one patient who suffered from severe...
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The gait of a patient with severe rigidity but no freezing. The EMG activity is similar to that of normal gait except for the increased background activity in both tibialis anterior (TA) and gastrocnemius-soleus (GS) muscles. Arrows indicate foot placement (↓) and lifting (↑).

The EMG recordings of gait appeared relatively normal during walking until the patient 'froze', when the tracings became completely abnormal. On attempting to walk around a chair or during mental activation these patients would lift their heels off the ground and then shuffle a distance of only a few inches at the time, the shuffling movement being performed commonly while the heel was off the ground. On occasions the patients fell onto their knees.

The electromyographic recordings were consistently the same in all patients. The onset of EMG activity in gastrocnemius-soleus was followed approximately 50–70 msec later by activity in tibialis anterior, which thus appeared to splint the limb. This coactivation of extensor and flexor muscles was associated with 'shuffling' which resulted in a deflection of the accelerometer trace (Fig. 4). EMG activity of extensor and flexor muscles of the knee during 'freezing' revealed

The gait of a patient when walking relatively normally (upper trace) is compared with blocking of gait or freezing in the same patient (lower trace). Freezing is associated with synchronous activity in gastrocnemius-soleus and tibialis anterior. Arrows in upper trace indicate foot lifting (↑) and placement (↓) as for Figs 1–3. Arrows in the lower trace mark shuffling of the foot associated with freezing.

The response to two years of L-dopa therapy in patients without features of dystonia. The graph of clinical improvement plotted over two years in four patients shows that initial improvement with L-dopa therapy was maintained. No patient was troubled by freezing of gait.
FLEXOR ACTIVITY SLIGHTLY BEFORE EXTENSOR ACTIVITY AND THEN COACTIVATION OF BOTH MUSCLES. ACTIVITY IN THE GASTROCNEMIUS-SOLEUS AND HAMSTRING MUSCLES PROBABLY GIVES THE CHARACTERISTIC POSTURE BEFORE 'FREEZING' WHICH IS FOLLOWED BY THE COACTIVATION OF FLEXORS AND EXTENSORS WHICH IS RESPONSIBLE FOR THE 'FREEZING'. IN DYSTONIA MUSCULUS LORUM DEFORMANS TONIC NON-RECIPROCAL, INCONSCIOUS ACTIVITY APPEARS IN AGONISTS AND ANTAGONISTS AND THIS DYSTONIA IS DIRECTLY STIMULATED BY POSTURAL EFFORT OR BY ATTEMPTED VOLUNTARY MOVEMENT (YANAGIOAWA AND GOTO, 1971). A SIMILAR RESPONSE TO A POSTURE OR VOLUNTARY ACTIVITY APPEARS TO HAVE OCCURRED DURING 'FREEZING' IN THIS STUDY.

EFFECT OF TWO YEARS' L-DOPA THERAPY

PATIENTS WITHOUT FEATURES OF DYSTONIA. IN THIS GROUP CLINICAL IMPROVEMENT WAS MAINTAINED OR IMPROVED AFTER SIX MONTHS OF THERAPY WITH L-DOPA DESPITE A REDUCTION IN L-DOPA DOSAGE IN SOME PATIENTS (FIG. 5, TABLE). AN IMPORTANT OBSERVATION IS THAT NONE OF THE FOUR PATIENTS WAS TROUBLED BY 'FREEZING'. A LONGER DURATION OF PARKINSON'S DISEASE WAS ASSOCIATED WITH LOWER DISABILITY SCORES BEFORE THE INITIATION OF L-DOPA THERAPY.

PATIENTS WITH FEATURES OF DYSTONIA. ONLY ONE OF NINE PATIENTS IN THIS GROUP MAINTAINED HIS INITIAL CLINICAL IMPROVEMENT TO L-DOPA THERAPY (FIG. 6). BEFORE L-DOPA THERAPY FOUR PATIENTS WERE SUBJECT TO 'FREEZING' AND THIS INITIALLY RESPONDED WELL TO L-DOPA THERAPY. IN TWO PATIENTS 'FREEZING' REAPPEARED ASSOCIATED WITH A GENERAL DETERIORATION. IN THREE PATIENTS 'FREEZING' APPEARED FOR THE FIRST TIME DURING L-DOPA THERAPY.

DISCUSSION

The observations on the gait of normal man reported here differ from those on the hind limb of the cat during unrestrained locomotion as described by ENGBERG AND LUNDBERG (1969).
Foot lifting in the cat is associated with EMG activity in semitendinosus, while in man EMG activity in the flexors of the knee is usually absent. This is not surprising considering the differences in the posture of the hind limb of cat and man. Engberg and Lundberg (1969) have suggested that stepping may require a centrally programmed alternating activity in flexor and extensor muscles on which proprioceptive reflexes are superimposed. Since muscles acting across two joints, which flex the hip and extend the knee have interconnections of type Ia nerve fibres in the spinal cord different from those of the flexors of the knee and ankle, the above workers have been able to explain the gait in the cat on the hypothesis mentioned above. The unmasking of alternating activity in flexors and extensors in man during preferential block of large nerve fibres supports this hypothesis. Recently, Goodwin, McCloskey, and Matthews (1972) have demonstrated that activity of group Ia afferent nerve fibre is probably important in proprioception, a role not previously ascribed to spindle endings. Although Engberg and Lundberg's hypothesis is restricted to activity of Ia afferent fibres in the spinal cord, long-loop reflexes involving the cerebellum could also be involved as the cerebellum receives a large projection of group Ia afferent fibres.

Parkinson's disease is generally described as having three cardinal features: bradykinesia, rigidity, and tremor. Denny-Brown has emphasized that flexion dystonia is an important feature late in the disease but other dystonic manifestations of idiopathic Parkinson's disease are poorly understood and their response to the long-term administration of L-dopa is unknown. Andrews et al. (1972) demonstrated flexion dystonia electromyographically in the lower limbs of most patients with Parkinsonism but not in the upper limbs. Although the flexed posture of Parkinson's disease improves with L-dopa therapy, some elements of flexor dystonia remain (Andrews and Burke, 1972). Rigidity is found predominantly in the flexor muscles of upper and lower limbs irrespective of the severity of the disease (Andrews et al., 1973). The present study demonstrates that the 'freezing' gait of Parkinson's disease is probably a manifestation of dystonia and occurs only when flexion dystonia is present.

Recently Thompson (1972) reported that 32% of his patients with Parkinsonism have lost some of their initial response to L-dopa therapy, the average onset of deterioration occurring after 18 months. A similar distressing observation has been noted in this brief study over two years, the limitation of the deterioration to the group with flexion dystonia, and 'freezing' of gait has been a prominent feature of this deterioration. Recently Neilson and Andrews (1973) have compared the reflexes elicited during passive manipulation of a limb with the reflex responses evoked during activity in athetosis and found the resting tonic stretch reflexes and action tonic stretch reflexes differed in sensitivity, pattern, duration, and timing. It is likely that a similar discrepancy also occurs in Parkinson's disease and that both the action stretch reflexes and dystonic manifestations contribute to bradykinesia.

Denny-Brown (1962) has postulated that the flexion dystonia of Parkinson's disease can be attributed to associated lesions in the globus pallidus. It is possible that such a pallidal lesion could deteriorate progressively, while synaptic transmission in the nigrostriatal pathway was improved by the use of L-dopa. This study suggests that the response to chronic therapy with L-dopa should be analysed in a large series, not only with respect to bradykinesia, rigidity, and tremor (including the resting alternating tremor and the action synchronous tremor of Parkinson's disease), but also with attention to the dystonic manifestations.

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